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REVIEW

Neural influences in colorectal cancer progression and therapeutic strategies

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Abstract

Purpose This review aims to elucidate the neural mechanisms driving colorectal cancer (CRC) growth, metastasis, and therapeutic resistance, summarizing the roles of neurotransmitters, neurotrophic factors, and neural signaling in carcinogenesis. It further explores therapeutic strategies targeting neural dependencies in CRC.

Methods A comprehensive PubMed search was conducted using the keywords colorectal cancer and tumor innervation, focusing on studies published between 2000 and 2024. The review synthesizes evidence across four domains: neurotransmitter-receptor interactions, gut-brain-microbiota axis dynamics, neuroimmune modulation, and neural regulation of cancer stem cells, discussing their collective impact on CRC pathophysiology.

Results Neural innervation significantly influences CRC progression. For instance, the neurotransmitter serotonin promotes tumor growth and metastasis via paracrine and autocrine stimulation, while neurotrophic mediators like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) activate oncogenic signaling through receptor tyrosine kinases (RTKs). Downstream pathways, such as Wnt/β-catenin signaling, are modulated by neural inputs, underscoring CRC's neurodevelopmental dependency and highlighting their potential as therapeutic targets.

Conclusion Neural mechanisms are pivotal in CRC progression, revealing novel therapeutic avenues. Strategies targeting neurotransmitter synthesis, neurotrophic signaling, or neuroimmune crosstalk may disrupt tumorigenic loops while preserving systemic nervous system integrity. Future research must prioritize translating these insights into clinical interventions to improve patient outcomes. Elucidating the intricate interplay between neural mediators and cancer pathogenesis, coupled with developing therapies specifically targeting the neurogenic basis of CRC aggressiveness, represents a critical frontier in oncology.

Keywords Colorectal cancer · Neural innervation · Gut-brain axis · Targeted therapy · Mechanism

Introduction

Colorectal cancer (CRC) pathogenesis has traditionally centered on genetic mutations and epigenetic dysregulation. However, emerging paradigms in neuro-oncological regulatory networks are reshaping our understanding of CRC biology by revealing the master regulatory role of the nervous system in tumor-microenvironment co-evolution. Recent studies demonstrate that the nervous system dynamically governs the entire trajectory of CRC initiation, invasion, and metastasis through multidimensional mechanisms—ranging from intrinsic tumor innervation to gut-brain-microbiome axis signaling and neuroimmune regulatory circuits. Its mechanistic underpinnings transcend the classical "passive diffusion" model of perineural invasion (PNI), instead

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actively modulating tumor cell proliferation and migration via neurotransmitter-receptor interactions (e.g., norepinephrine and acetylcholine) and remodeling neurotrophic factor-driven tumor innervation and angiogenesis (e.g., altered expression of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF)). This bidirectional neuro-cancer interplay positions neural regulation as an indispensable axis in CRC progression and a novel therapeutic frontier.

This review establishes a conceptual framework to delineate neuro-oncological dynamics. First, it elucidates the intricate reciprocity between de novo neurogenesis and neoplastic evolution, emphasizing the trophic influence of neurotransmitters, neurotrophic factors, and neural signaling pathways on tumor growth. Second, it interrogates the pathogenic contributions of the microbiome-gut-brain axis, neuroendocrine communication, and neuroimmune crosstalk in CRC pathogenesis. Thirdly, by highlighting the cardinal role of neural activity in sculpting tumor biology—particularly through driving cancer stem cell self-renewal, niche formation, and metastatic dissemination—this work proposes precision neuro-oncology strategies that selectively target tumor-addicted neural dependencies while preserving systemic neural integrity. Such approaches may circumvent resistance mechanisms inherent to traditional therapies (e.g., EGFR inhibitors) and pioneer transformative combinatory regimens.

Global burden and epidemiological significance of colorectal cancer

According to the 2020 Global Cancer Statistics published by the International Agency for Research on Cancer (IARC), CRC imposes a substantial global burden: approximately 1.93 million new cases (accounting for 10.0% of total cancer cases) and 935,000 deaths (9.4% of total cancer-related deaths) were reported worldwide, placing CRC third in incidence and second in mortality among all malignancies [1]. Although age-standardized incidence rates (ASIR) of CRC have shown a declining trend in some high-income countries due to the implementation of standardized screening programs, recent studies highlight a rapid increase in early-onset colorectal cancer (defined as cases diagnosed before age 50) in Western nations [2]. Despite substantial advancements in CRC diagnosis and targeted therapies over the past decades, the regulatory networks within its tumor microenvironment remain incompletely elucidated. Notably, emerging research has identified the critical role of tumor innervation within the tumor microenvironment. Therefore, systematically deciphering the molecular mechanisms underlying neural regulation in CRC will provide a theoretical foundation for developing innovative targeted therapies and hold significant translational value for improving patient prognosis.

Neuroanatomy and function innervation of the colorectum

The innervation of the colon and rectum is rather complex, and the nervous system can be divided into two parts: the extrinsic and intrinsic nervous systems. The extrinsic nervous system consists of the sympathetic and parasympathetic nerves, while the intrinsic nervous system is the enteric nervous system (ENS), which is unique to the intestine. Regarding sympathetic innervation, the right colon and appendix are innervated by fibers from the superior mesenteric ganglion, which release norepinephrine, ATP, and neuropeptide Y, thereby delaying intestinal transit and secretion, inhibiting smooth muscle contraction, and causing intestinal vasoconstriction [3]. The left colon (including the transverse colon, descending colon, and sigmoid colon) and the upper rectum are innervated by fibers from the inferior mesenteric ganglion, exerting similar inhibitory effects. As for the parasympathetic nerve, the colon is innervated by the vagus nerve and sacral efferent nerves from the central nervous system. The vagus nerve descends to the pre-aortic plexus and follows the colonic branches of the superior mesenteric artery, acting on the cecum, ascending colon, and most of the transverse colon. The sacral efferent nerves can reach as high as the left colic flexure. They mainly release acetylcholine to exert excitatory or inhibitory regulation on gastrointestinal tone and motility. The sympathetic nerve fibers of the rectum originate from the L1–L3 segments and form the lumbar sympathetic nerve after passing through the sympathetic ganglia. The parasympathetic nerve is managed by the pelvic splanchnic nerve, and their fibers converge into the pelvic plexus on the pelvic side wall. The neurons of the ENS are distributed in thousands of small ganglia, mainly concentrated in the submucosal and myenteric plexuses [4].

This system has complete reflex pathways and can control intestinal contraction, regulate local blood flow, and the movement pattern of fluid through the mucosa. It also collaborates with the intestinal endocrine and immune systems to play a role in nutrient absorption and maintaining the mucosal barrier [5]. Additionally, the brain-gut axis (BGA) reveals the bidirectional regulatory relationship between the brain and the gut in gastrointestinal function and the gut-brain pathway. The intestine can synthesize and secrete neuroactive molecules that cross the blood–brain barrier to affect the central nervous system. At the same time, neuroactive molecules from the brain can also act on the intestine through the sympathetic and parasympathetic nervous systems or humoral pathways to regulate its function [6].

Abnormal neural innervation in colorectal cancer

Comparative survival rates of colorectal cancer patients show that those with positive sympathetic nerve expression have a better prognosis than those with negative sympathetic nerve expression. As parasympathetic nerve and α− 9nAChR expression increase in colorectal cancer tissue, patient prognosis worsens, indicating that parasympathetic nerves promote advanced colorectal cancer progression through α− 9nAChR [7]. The sympathetic nervous system activates β-adrenergic receptors by secreting norepinephrine, thereby stimulating tumor cell proliferation. The parasympathetic nervous system stimulates tumor cell invasion and metastasis by secreting acetylcholine to activate M receptors. Studies have shown that chemical sympathectomy using 6-hydroxydopamine (6-OHDA) can reduce the incidence of azoxymethane (AOM)-induced colorectal cancer in rats [8]. In advanced colorectal cancer, compared to removing sympathetic nerves, removing parasympathetic nerves reduces tumor incidence, volume, and weight and decreases proliferation cell nuclear antigen and Ki- 67 immunostaining, indicating inhibition of tumor cell proliferation. Removal of parasympathetic nerves also downregulates vascular endothelial growth factor and CD31 expression, effectively inhibiting tumor angiogenesis in rat colon tissue. Additionally, expression levels of nerve growth factor, M3 receptors, and β− 2 adrenergic receptors in tissue are significantly reduced [9]. In summary, sympathetic nerves are more prevalent in early-stage cancer with a better prognosis, while parasympathetic nerves are more prevalent in late-stage cancer with a poorer prognosis.

The role of the nervous system in tumor development

The nervous system plays a crucial role in the progression of tumors, exerting regulatory effects through various mechanisms. Cancer cells in head and neck cancers (with p53 mutation) secrete miRNA-miR- 43a within vesicles, driving the reprogramming of cancer-associated sensory neurons into adrenergic neurons, similar to sympathetic neurons [10]. Similar mechanisms in prostate and pancreatic cancers suggest that cancer cells aim to guide nerve innervation through the expression of chemorepellent/attractant and axon guidance molecules. On the other hand, cancer cells can also exhibit attenuated nerve innervation, for instance, head and neck cancer cells release vesicles (exosomes) containing EphrinB1, which can induce nerve fiber growth, thus blocking exosome release weakens tumor nerve innervation [11].

Tumor progression induces stromal reactivity, upregulating cytokine production by resident fibroblasts nearly as same as NE, suggesting that the ability of fibroblasts to coordinate neoangiogenesis and maintain inflammation in the vitreous is enhanced with the release of catecholamines. Some certain cytokines enhance β 3-AR expression in melanoma cells, while β 2-AR is upregulated by cytokines, thus suggesting a feed-forward loop between NE and its cognate receptors. In cancer, adrenergic signaling from tumor cells induces the release of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), increasing nerve density in the tumor area. This in turn leads to increased adrenergic signaling, resulting in norepinephrine accumulation, activation of β-adrenergic receptors, and remodeling of the extracellular matrix of cancer-associated fibroblasts (CAFs). This remodeling will further support tumor growth [12–14] (Fig. 1).

In gliomas, specific synaptic connections can also be established between neurons and cancer cells. Here, neurons surrounding the tumor secrete neural glial protein- 3, promoting the formation of neuron-glioma synapses with specific types of AMPA receptors on glioma cells [15]. The activation of these neurons promotes cancer growth by releasing glutamate salts to stimulate glioma cell proliferation and invasion. Furthermore, the activation of AMPA receptors on glioma cells stimulates the self-release of glutamate, thus activating AMPA receptors in an autocrine manner and further activating neurons.

Neurogenic regulation promotes colorectal cancer progression

Despite the growing interest in the role of neurons in cancer, the passive role of neurons in perineural invasion (PNI) has been extensively studied in CRC and other cancer types, where tumor cells utilize nerve fibers as conduits for migration to distant sites, contributing to rapid tumor growth and metastasis. However, knowledge regarding the role of the enteric nervous system in CRC remains limited.

Cancer cells can induce their own neurogenic regulation, which is inevitably influenced by external factors. Additionally, it has been established that neuropeptide Y (NPY), produced by enteric neurons, plays a role in regulating intestinal inflammation, and cancer cells can signal to neuronal cells [16].

Active communication between cancer cells and neuronal cells has been described in various cancer types, and experimental manipulation of neuronal signaling has shown that neurons can influence carcinogenesis. In cancer animal models, enhancing sympathetic nervous system activation has been shown to promote tumor growth and cancer progression [17], while reducing parasympathetic nervous system activity in the stomach inhibits tumor formation. In cancer-prone mouse models (ApcMin/+ model), vagus nerve ablation reduced tumor size, indicating that exogenous neurogenic regulation from the vagus nerve can promote cancer

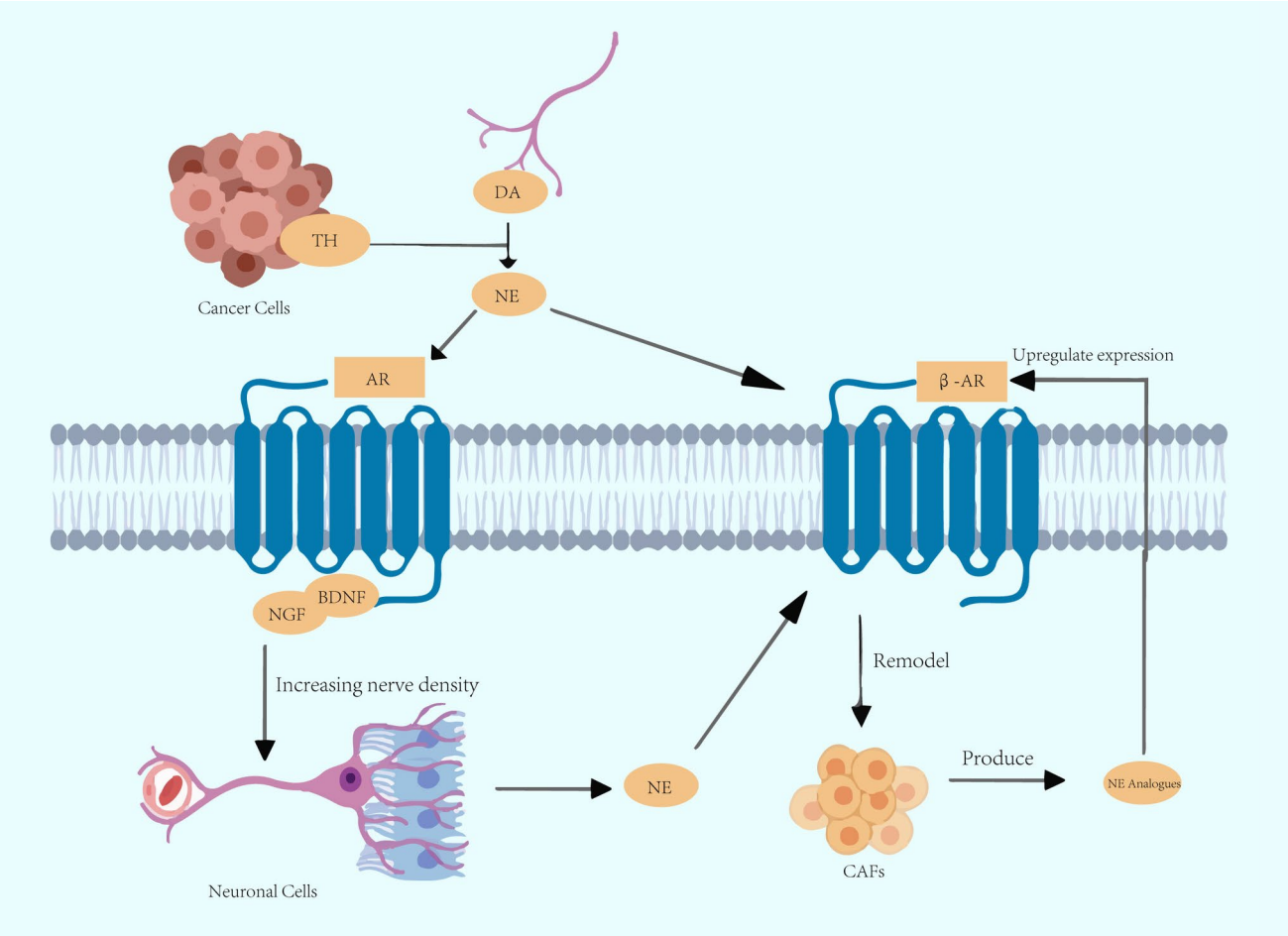

Fig. 1 Specific crosstalk between cancer and neuronal cells. Adrenergic signaling in tumor cells induces the release of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), augmenting neural density within tumor regions. This heightened innervation amplifies adrenergic pathway activity, resulting in norepinephrine (NE) accumulation. NE activates β-adrenergic receptors (β-ARs) and reprograms cancer-associated fibroblasts (CAFs), which subsequently secrete NE-mimetic cytokines. These cytokines further upregulate β-AR expression on tumor cells, establishing a self-perpetuating loop that drives tumor progression

development [18]. Conversely, in the same study, surgical sympathetic denervation at the level of the superior mesenteric artery did not suppress tumor growth, suggesting that the mode of action of specific nerves rather than neuronal activity itself may influence carcinogenesis.

Neurogenic regulation promotes colorectal cancer brain metastasis

The concept of the gut-brain axis was proposed as early as the 1960 s, and with further research on microbiota, it has been recognized that the gut microbiota plays a crucial regulatory role in the interaction between the brain and the gastrointestinal tract, leading to the creation of the term "microbiota-gut-brain axis" [19]. The brain tightly links gastrointestinal function and brain function through bidirectional neural-endocrine-immune networks via CNS, ENS, and HPA. The gut can synthesize and release a range of neuroactive molecules that can cross the blood–brain barrier and affect central nervous system function. Similarly, some neuroactive molecules can be transmitted from the brain to the gut through the sympathetic and parasympathetic nervous systems or humoral pathways. For a long time, the gut-brain axis has been considered a mediator of stress-related gastrointestinal symptoms. However, the interaction between the brain and gut extends far beyond stress, anxiety, or depression and should also include diseases that are affected by the same pathological influences on the brain, gut, and their connection through the autonomic nervous system.

The brain may regulate gastrointestinal tumors through two pathways: anatomical neural pathways and neuroendocrine pathways. Stimulation and deactivation of the central nervous system, sympathetic nervous system, and parasympathetic nervous system, or alterations in gastrointestinal

neurogenic regulation, may lead to a high incidence of colon cancer. When the gut-brain axis is activated by tumor cells, the brain responds to cancer cells through neuroendocrine-immune and behavioral reactions, including neuropeptide metabolism, regional brain stimulation, and behavioral changes [20, 21]. Furthermore, neurotransmitters and neurotrophic factors can have stimulatory or inhibitory effects during the progression of colorectal cancer [22].

Neurotransmitters in tumor growth

During the process of tumor growth, cancer cells and the surrounding nervous system are able to release a large number of neurotransmitters into the tumor microenvironment. These neurotransmitters can excite relevant receptors and influence multiple cell signaling pathways, playing a crucial role in the proliferation and progression of cancer. There is increasing evidence supporting the role of neurotransmitters in the development of colorectal cancer.

Dopamine (DA)

DA is a type of monoamine neurotransmitter that primarily exerts its functions through dopamine receptors (DR) present in various organs and cells throughout the body. These DR can be divided into two groups: D1-type receptors (including D1 and D5) and D2-type receptors (including D2, D3, D4) [23, 24]. Previous studies have found that dopamine can regulate the differentiation of CD8 + cells into CD103 + tissue-resident memory CD8 + T cells, thereby modulating the induction of anti-colorectal cancer immunity by tissue-resident memory CD8 + T cells [25]. Research has reported that activation of dopamine receptors D1 (DRD1) and D5 (DRD5) can inhibit growth by suppressing the Akt/mTOR signaling pathway [26]. An animal experiment has shown that DA can inhibit VEGF-mediated angiogenesis and enhance the efficacy of anticancer drugs such as 5-fluorouracil, playing an important role in inhibiting colorectal cancer cell proliferation and promoting apoptosis [27]. DARPP-32, as a protein involved in regulating the dopamine and cAMP signaling pathways in the brain, its overexpression can promote colorectal cancer cell proliferation, migration, invasion, and reduce apoptosis [28]. In addition, activation of DRD1 and DRD5 inhibits the growth of various tumors, including but not limited to colorectal cancer, by inhibiting the Akt/mTOR signaling transduction [26].

In conclusion, neurotransmitters, particularly dopamine, play a significant role in the development and progression of colorectal cancer. Understanding the intricate interplay between neurotransmitters and cancer biology may provide valuable insights for developing novel therapeutic strategies targeting the neuro-cancer interaction.

Acetylcholine (Ach)

Ach is an important neurotransmitter that plays a variety of biological functions in the central and peripheral nervous systems. In addition to its role in neurotransmission, Ach also plays a significant role in other tissues and organs, including the intestines. Acetylcholine receptors are mainly divided into muscarinic Ach receptors and nicotinic Ach receptors. Activation of nicotinic Ach receptors can promote proliferation and reduce apoptosis of colorectal cancer (CRC) cells [29]. The α7 subtype of nicotinic Ach receptor (α7nAChR), as a major subtype, exhibits dual roles in CRC progression depending on tumor stage. While early studies suggested its overexpression in CRC cells promotes proliferation and migration through nicotine-mediated signaling [30], recent evidence indicates that α7nAChR may paradoxically inhibit metastasis in advanced CRC by suppressing epithelial-mesenchymal transition (EMT) pathways [30]. Nicotine and tobacco-specific carcinogens enhance the proliferation and migration of CRC cells through the mechanism of α7 subtype of nicotinic Ach receptor signaling [31].

The muscarinic receptor family is a class I G protein-coupled receptor, consisting of five muscarinic receptors (MR) subtypes, known as M1R-M5R [32]. These subtypes are expressed in various organs and tissues, playing different or overlapping functions, including smooth muscle contraction and regulation of ion channels. The distribution pattern of MR subtypes varies in different organs. In intestinal epithelium, M1R and M3R are mainly expressed. Numerous experimental data demonstrate that blocking M3R can effectively attenuate tumor growth in colorectal cancer [33]. Currently, only two endogenous ligands for M3R are known: acetylcholine (ACh) and specific bile acids and their derivatives. In the past, acetylcholine was considered a neurotransmitter secreted by neurons, but recent studies have shown that ACh can also be produced and secreted by normal non-neuronal cells and tumor non-neuronal cells, and this non-neuronal ACh can also exert corresponding physiological functions.

In some cancers such as CRC, cancer cells can also produce ACh, and non-neuronal ACh may even be the main source of ACh, serving as an autocrine growth factor for CRC [34]. In the process of M3R-mediated intestinal tumor formation and CRC progression, the transactivation of epidermal growth factor receptor (EGFR) is a key mechanism [35]. After binding with ACh, M3R excites downstream protein kinase C-α (PKC-α), which then activates Src and p38-α (a member of the mitogen-activated protein kinase family). Steroid receptor coactivator (Src) binds to EGFR through the mitogen-activated protein kinase kinase (MEK) and extracellular regulated protein kinases 1/2 (ERK1/2) pathway to stimulate signal transduction. p38-α

and ERK1/2 coordinately induce matrix metalloproteinase 1 (MMP1) gene transcription and enhance MMP1 protein expression [36]. The generated MMP1 can degrade the extracellular matrix, promoting tumor invasion and metastasis. The enhanced release of MMP1 in the colorectal cancer cell microenvironment may catalyze the release of EGFR ligands and further enhance EGFR activation [36], inducing the transcriptional activation of many genes related to CRC (cyclooxygenase- 2, cyclin D1, etc.). These findings suggest that a combination therapy targeting EGFR activity alongside inhibitors of M3R, PKC-α, or p38-α signaling pathways may hold significant therapeutic potential in preventing or delaying colon cancer metastasis and inhibiting cancer cell dissemination. Future research should prioritize investigating the efficacy of such combinatorial approaches, specifically evaluating the synergistic effects of EGFR inhibitors in conjunction with M3R, PKC-α, or p38-α inhibitors in the context of colon cancer progression. There is also evidence that the binding of M3R with ACh can directly activate matrix metalloproteinase MMP7, catalyzing the release of HBEGF, a ligand for EGFR [37]. The binding of HBEGF to EGFR activates downstream ERK signaling, inducing the transcriptional activation of many genes related to CRC progression, as well as inducing the transcription of MMP1, MMP7, and MMP10 genes [37]. This forms a positive feedback mechanism.

In addition to ACh, bile acids and their derivatives are also important ligands for M3R. The proliferation of colorectal cancer cells induced by bile acids operates through the same mechanism as that induced by ACh. This confirms the association between elevated fecal bile acids and the occurrence of CRC, explaining how excessive consumption of fatty and greasy foods does indeed increase the risk of CRC and providing effective strategies for CRC prevention and treatment. Furthermore, muscarinic receptor 1 (M1R) has been found to be downregulated in colorectal cancer [38], suggesting a protective role of M1R in colorectal cancer.

γ-Aminobutyric acid (GABA)

GABA plays a major role in exerting neuronal inhibitory effects in the central nervous system and has diverse functions in the enteric nervous system and enteroendocrine cells of the gastrointestinal tract. GABA can influence the proliferation, migration, and invasion capabilities of colorectal cancer (CRC) cells by acting on GABA receptors in intestinal tissues, including GABA-A and GABA-B receptors, particularly the GABA-B receptor. Research by Huang et al. revealed higher expression of GABA in colorectal cancer compared to normal colonic tissue [39]. Furthermore, it was found that GABA binding to the GABA-B receptor leads to enhanced β-catenin signaling, thereby promoting CRC cell proliferation and inhibiting infiltration of CD8 + T lymphocytes, resulting in immune suppression [39]. Studies have reported that GABA can reduce proliferation and increase apoptosis of 5-fluorouracil-resistant HT29 colorectal cancer cells, while having no significant effect on parental HT29 colorectal cancer cells [39]. Notably, the immunemodulatory effects of GABA are increasingly recognized. Animal studies show GABA-A receptor blockade enhances CD8 + T cell infiltration and synergizes with anti-PD1 therapy, suggesting combinatorial immunotherapy potential [40]. However, a study indicated that GABA activation of GABA-B receptors can inhibit the migration of colon cancer cells in vitro [41].

Adrenaline/noradrenaline

Recently, catecholamines have been found to be involved in the regulation of cancer occurrence and progression in various cancer types such as breast cancer, lung cancer, and pancreatic cancer [42]. Adrenaline and noradrenaline play crucial roles in regulating physiological and pathological processes in the human body. It has been reported that adrenaline signaling is upregulated in colorectal cancer, exerting effects on the proliferation, migration, and invasion capabilities of colorectal cancer cells by acting on adrenergic receptors, particularly the β2-adrenergic receptor [43, 44]. Adrenaline can suppress CD8 + T lymphocyte proliferation and interferon-γ production by increasing cyclooxygenase- 2 and interleukin- 10 expression in macrophages, thereby promoting immune evasion in colon cancer [45]. Furthermore, evidence suggests that noradrenaline activates the CREB1/miRNA- 373 axis by inducing phosphorylation of cAMP response element-binding protein 1 (CREB1), promoting proliferation and metastasis of colon cancer cells [44]. The neurotransmitter adrenaline promotes proliferation of human colon cancer cell line HT- 29 by inducing the expression of cyclooxygenase- 2, VEGF, prostaglandin E2, and MMP- 9 [46]. Pu et al. found that adrenaline can promote proliferation and increase chemoresistance of colon cancer HT29 cells by inducing miR- 155 [42]. The β2-adrenergic receptor (ADRB2) emerges as a key mediator of catecholamine effects in CRC. A phase II clinical trial (NCT03117946) investigating propranolol (ADRB2 antagonist) combined with chemotherapy showed a 30% improvement in progression-free survival, validating preclinical findings [44].

5-Hydroxytryptamine (5-HT)

5-HT, also known as serotonin, is a monoamine inhibitory neurotransmitter with high levels in the cerebral cortex and synaptic nerve terminals, produced from the essential amino acid tryptophan metabolism. In the gastrointestinal tract, 5-HT is synthesized by two types of cells: enterochromaffin cells in the mucosa and enteric 5-hydroxytryptamine

neurons distributed in the intestinal wall. 5-HT exerts its biological functions by binding to its corresponding receptors [47].

Recent studies have found that 5-HT is overexpressed in colorectal cancer tissues and can promote the self-renewal of colorectal cancer stem cells and tumor formation [47, 48]. The high expression of 5-HT is significantly associated with lymph node metastasis in advanced colorectal cancer [49]. Research by Li et al. has demonstrated increased biosynthesis and secretion of 5-HT in colorectal cancer cells, and excessive production of 5-HT in macrophages has been shown to activate the NLRP3 inflammasome. Meanwhile, the NLRP3 inflammasome-mediated release of IL- 1β leads to increased biosynthesis of 5-HT in colorectal cancer cells, forming a positive feedback loop between 5-HT and NLRP3 signaling in the colorectal cancer microenvironment, thereby promoting the development of colorectal cancer [49].

Colorectal cancer stem cells (CSCs) are a subset of cells within colorectal cancer that can self-renew and differentiate, closely associated with the occurrence, metastasis, invasion, drug resistance, and recurrence of colorectal cancer [50]. 5-HT directly binds to CSC receptors such as 5-HT receptors 1B, 5-HT receptors 1D, and 5-HT receptors 1 F in a non-Ach dependent manner, activating the Wnt/β-catenin signaling pathway, promoting CSC self-renewal, and tumor formation [47]. Furthermore, the serotonin transporter (SERT) plays a crucial role in the development of colorectal cancer. SERT transports 5-HT into colorectal cancer cells, activating the RhoA/ROCK/YAP signal, enhancing Yes-associated protein (YAP) expression, and promoting the growth of colon cancer cells [51].

In individuals with a family history of colorectal cancer, the use of selective serotonin reuptake inhibitors (SSRIs), such as antidepressants, can significantly reduce the risk of developing colorectal cancer. The association with late-stage colorectal cancer is more significant than early-stage colorectal cancer, and the association with rectal cancer is stronger than colon cancer [52]. Therefore, SSRIs may become one of the effective treatment methods for colorectal cancer.

5-HT also mediates the immune system to promote tumor growth. Studies have shown that elevated levels of 5-HT activate lymphocytes to release a large number of cytokines, creating a pro-inflammatory microenvironment that promotes the development of colorectal cancer [53]. Conversely, another study in TPH1 gene knockout mice showed that a decrease in 5-HT levels led to increased colon DNA damage, suggesting that 5-HT plays a key role in protecting the intestinal tract and preventing tumor development by promoting DNA repair in early colorectal tumors [54].

In conclusion, 5-HT is a highly promising molecular therapeutic target. After fully understanding its specific functions, selective targeting of 5-HT receptors and selective serotonin reuptake inhibitors may become effective treatments for CRC.

Blood vasoactive intestinal peptide (VIP)

VIP is a neuropeptide with vasodilatory activity. It has two receptors, VPAC1 and VPAC2, which are II-type G protein-coupled receptors belonging to the secretin receptor family. VPAC1 is typically expressed in the epithelial cells of the gastrointestinal tract, while VPAC2 is expressed in the smooth muscle of the gastrointestinal tract [55]. Multiple studies have reported elevated serum VIP levels in colorectal cancer (CRC) patients, which can promote the proliferation and spread of CRC cancer cells [56]. VIP may become a molecular target in the treatment of CRC.

Research indicates that VPAC1 is often overexpressed in colon cancer cells and is associated with the degree of tumor differentiation: 35% in well-differentiated colon cancer, 65% in moderately differentiated colon cancer, and 87% in poorly differentiated colon cancer [55]. The level of VPAC1 can be measured to predict the degree of tumor differentiation.

Previously, VIP was thought to promote CRC and tumor cell proliferation by inducing the cAMP-Rap1/Ras-B-Raf-ERK pathway [57]. However, recent studies have found that VIP can also transactivate EGFR. VIP can bind with prostaglandin E2 (PGE2) to rapidly activate PKA, leading to phosphorylation of naked cuticle homolog 2 (NKD2) at the Ser- 223 site [58]. This phosphorylation stabilizes NKD2, promoting the delivery of transforming growth factor-α (TGFα) to the cell surface, resulting in increased EGFR activation and the transcriptional activation of many genes associated with colorectal tumor progression [58]. Cao et al. introduced the GPCR ligand VIP to Caco- 2 cells to investigate its role in GPCR-mediated EGFR transactivation. Notably, parental Caco- 2 cells did not express TGFα. In the absence of TGFα induction, the addition of VIP had no significant effect on EGFR activity. However, in the TGFα-induced state, EGFR activity exhibited a sharp increase within 1 min following VIP administration. These findings suggest that GPCR-mediated transactivation of EGFR is primarily driven by enhanced cell surface delivery of TGFα. Consequently, both the delivery and proteolytic processing of EGFR ligands may be regulated by GPCR agonists to potentiate EGFR signaling [58]. Further studies are warranted to explore whether other GPCR ligands exhibit similar mechanisms of action and to elucidate their potential preferences in modulating EGFR activity. Further research is needed to determine if this EGFR transactivation mode is stably expressed in CRC cancer cells.

VPAC1 can serve as a target for anticancer drugs, as VPAC1 antagonists inhibit the growth of colon cancer cell lines in vitro [55]. KS- 133, a specific antagonist of VIPR2,

has great therapeutic potential and can promote cancer immune activation and induce anti-tumor effects, whether used alone or in combination with immune checkpoint inhibitors [59].

Neurotrophic factors

Neurotrophic factors are a class of protein molecules that promote the growth, differentiation, and survival of nerve cells, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) [60]. Recent studies have shown that neurotrophic factors not only play important roles in the nervous system but also regulate cancer development. It has been reported that NGF plays a role in the metastasis of colorectal cancer by promoting the phosphorylation of tropomyosin-related kinase A (TrkA) and activating the MAPK/ERK signaling pathway. Additionally, NGF expression in colorectal cancer tissue is associated with tropomyosin-related kinase A, MMP2, and MMP9 proteins [61]. BDNF has been found to be increased in colorectal cancer tissue and is associated with tumor growth, metastasis, and resistance to apoptosis [62, 63]. BDNF binds to the tropomyosin-related kinase B (TrkB) receptor, activating a signaling pathway similar to NGF, which promotes the growth and invasion of colorectal cancer cells [62]. Furthermore, BDNF and TrkB are overexpressed in colorectal cancer compared to non-colorectal cancer tissue, especially in advanced colorectal cancer. BDNF/TrkB signaling shows stage-specific prognostic value. A study revealed high TrkB expression correlates with poor differentiation and liver metastasis, but not with early-stage survival [64] (Table 1).

The role of neural innervation in the tumor microenvironment (TME)

Increased sympathetic nerve innervation in solid tumors is driven by the secretion of neurotrophic factors from malignant cells, which activate the β-adrenergic receptor (β-AR) signaling pathway. This has been extensively confirmed by in vivo studies and mouse models. For instance, Tan et al. demonstrated that pancreatic cancer and cholangiocarcinoma exhibit significant nerve fiber infiltration, with upregulation of neurotrophic factors such as NGF and BDNF, leading to enhanced tumor progression and metastasis [65]. In contrast to the tumor-promoting effects of sympathetic signaling, parasympathetic nervous signals have been shown to exert inhibitory effects on tumor growth, although their role remains less explored [66].

The role of sympathetic nerve innervation extends beyond tumors to primary and secondary lymphoid organs, such as the spleen and lymph nodes, where it modulates inflammatory responses by regulating immune cell activity through neurotransmitter-receptor interactions. Wang et al. highlighted that norepinephrine released from sympathetic nerves binds to β2-AR on immune cells, suppressing anti-tumor immunity and promoting an immunosuppressive tumor microenvironment (TME) [67]. This direct regulation of the immune system by the autonomic nervous system suggests that targeting neuron-immune cell communication could be a promising therapeutic strategy to reprogram the TME.

In the TME, Schwann cells undergo adaptive reprogramming in response to nerve damage caused by tumors, acquiring repair phenotypes similar to those observed during nerve regeneration. This process is closely linked to increased nerve innervation in cancer. For example, Ceyhan et al. reported that pancreatic cancer induces "neural remodeling," characterized by altered innervation patterns and increased Schwann cell activity, which contributes to tumor progression and pain [68].Additionally, studies on the sympathetic nervous system's role in mucosal immunity have shown that loss of sympathetic input leads to a pro-inflammatory state, compromising epithelial barrier function while enhancing antimicrobial defenses.

Interplay between the nervous and immune systems

The central nervous system controls numerous non-neuronal cells and physiological functions of the body, either through hormone secretion into the bloodstream or via the peripheral nervous system in a more region-specific manner. The peripheral nervous system connects the central nervous system to all organs, including lymphocytes, through the sympathetic nervous system (adrenergic), parasympathetic nervous system (cholinergic), motor, and/or sensory nerve fibers [69].

The sympathetic nerves run along the vascular system and separate from it upon entering lymphoid organs. They terminate upon close contact with T lymphocytes and plasma cells, forming so-called "neuroeffector junctions" [70]. The nerve fibers that innervate lymphoid organs can secrete various neurotransmitters and neuropeptides, including vasoactive intestinal peptide, neuropeptide Y, substance P, enkephalin, and neurotensin [71]. Corresponding neurotransmitter receptors are also expressed on immune cells.

The immune cells respond to neurotransmitters and neuroregulatory agents, and conversely, nerve cells can also respond to signaling molecules from the immune system. For a long time, the predominant consideration was the long-term interaction between the immune system and the brain through hormone-like factors. However, current research is increasingly focusing on short-term interactions based on immune factors produced by local nervous systems.

Table 1 Neurotransmitter pathways in colorectal cancer

Ref. no	Neurotransmitters studied	Results obtained	Model used	Key findings
26	Norepinephrine, ATP, neuropeptide Y	Sympathetic nerves delayed intestinal transit and secretion, inhibited smooth muscle contraction, and caused intestinal vasoconstriction	Human tissue samples	Sympathetic innervation of the colon and rectum
27	Neural fibers	Parasympathetic anatomical studies demonstrated the complex structural organization of the enteric nervous system (ENS), particularly the subdivision of the submucosal plexus into three distinct compartments	Human tissue samples	Integrated central control through the ENS, CNS, and sympathetic ganglia coordinates the synergistic action of the intestinal nervous, endocrine, and immune systems
28	Serotonin	Brain-gut bidirectional regulatory relationships in gastrointestinal function and the gut-brain axis	Extensive literature review	Neural and endocrine control of digestion are tightly coordinated
29	Serotonin	Role of the gut-brain axis in regulating intestinal and central nervous system functions	Extensive literature review	The gut-brain axis plays a role in both intestinal and CNS functional regulation
30	α9 nicotinic acetylcholine receptor (α9-nAChR)	Expression of autonomic nerves and α9-nAChR in colorectal cancer (CRC) and their clinical significance	Human tissue samples	α9-nAChR is highly expressed in CRC tissues, suggesting its association with tumor progression
31	6-Hydroxydopamine (6-OHDA)	Chemical sympathectomy using 6-hydroxydopamine (6-OHDA) reduced the incidence of azoxymethane (AOM)-induced CRC in rats	AOM-induced CRC model in Wistar rats	6-OHDA exerts protective effects against colon carcinogenesis, implying significant roles of sympathetic activity in CRC development
33	Sympathetic and parasympathetic nerves	Parasympathetic (but not sympathetic) denervation led to significant reductions in tumor incidence, volume, weight, cell proliferation (PCNA/Ki- 67 staining), angiogenesis (CD31/VEGF), and downregulation of NGF, β2-adrenergic, and M3 receptors	Male Wistar rats	Parasympathetic denervation may critically impact colon carcinogenesis and potentially serve as a therapeutic strategy for advanced CRC
34	Adrenergic nerves	Loss of TP53 caused adrenergic transdifferentiation of tumor-associated sensory nerves via miR- 34a deficiency	Mouse oral cancer model	Mechanisms underlying the reprogramming of tumor-associated neurons to an adrenergic phenotype
35	Dopamine (DA)	DRD5 agonist SKF83959 is a potent inhibitor of tumor cell growth across multiple cancer types	Human tumor cell cultures	Activation of DRD1 and DRD5 suppresses tumor growth by inhibiting Akt/mTOR signaling
36	Dopamine (DA)	Dopamine combined with anticancer drugs significantly inhibited tumor growth and prolonged survival	MCF- 7 (breast) and HT29 (colon) tumor-bearing mice	Dopamine enhances the efficacy of conventional anticancer drugs, potentially acting as an anti-angiogenic agent in breast and colon cancer

Table 1 (continued)

Ref. no	Neurotransmitters studied	Results obtained	Model used	Key findings
37	Dopamine (DA)	Overexpression of DA-regulated phosphoprotein DARPP- 32 promoted cancer cell proliferation, migration, invasion, and reduced apoptosis	CRC cell lines	DARPP- 32 drives CRC progression via the PI3 K/AKT signaling pathway
38	Acetylcholine (ACh) and adrenaline/noradrenaline (Adr/NE)	Nicotine stimulated HT- 29 cell proliferation through α7-nAChR-mediated upregulation of catecholamine synthesis, ultimately activating β-adrenergic pathways	HT- 29 human colon adenocarcinoma cells	Mechanisms of α7-nAChR and β-adrenergic receptors in colon cancer tumorigenesis
39	Acetylcholine (ACh)	Dual roles of α7-nAChR in inflammation-associated gastrointestinal cancers	In vitro cell models	α7-nAChR exhibits context-dependent pro- or anti-tumor effects in intestinal cancers
40	Acetylcholine (ACh)	α7-nAChR mediated nicotine-enhanced colon cancer cell migration and upregulated fibronectin expression. COX- 2 signaling was induced by nicotine and contributed to fibronectin expression	Colon cancer cells	Nicotine and tobacco-specific carcinogens promote CRC proliferation and migration via α7-nAChR signaling
41	Acetylcholine (ACh)	M3R blockade exerted significant anti-tumor effects via multiple mechanisms, including immunosuppressive molecule inhibition, enhanced anti-tumor immunity, and suppressed angiogenesis through AKT/ERK inhibition	CT- 26 mouse colon cancer cells (in vitro and in vivo)	Crosstalk exists between the cholinergic and immune systems, influencing cancer immune evasion
42	Acetylcholine (ACh)	H508 human colon cancer cells produce acetylcholine (ACh)	H508 human colon cancer cells	ACh acts as an autocrine growth factor in colon cancer
43	Acetylcholine (ACh)	Interaction of cholinergic ligands with M3 muscarinic receptors in H508 cells induced EGFR transactivation, stimulating cellular proliferation	H508 human colon cancer cells	EGFR transactivation is a critical mechanism in M3R-mediated intestinal tumorigenesis and CRC progression
44	Acetylcholine (ACh)	Novel functional interactions between post-muscarinic receptor signaling pathways enhance MMP1 expression and drive colon cancer invasion	Human colon cancer cells	MMP1 degrades extracellular matrix, promoting tumor invasion and metastasis
45	Acetylcholine (ACh)	MMP7-catalyzed HBEGF release mediates ACh-induced EGFR transactivation and subsequent CRC proliferation	H508 human colon cancer cells	ACh binding to M3R directly activates MMP7 to release HBEGF, an EGFR ligand
46	Acetylcholine (ACh)	CHRM1/M1R serves as a critical deterrent in colon cancer development and progression	TCGA-COAD samples	Protective role of M1R in CRC
47	γ-Aminobutyric acid (GABA)	GABA-mediated β-catenin activation stimulated tumor cell proliferation and inhibited intratumoral CD8 + T cell infiltration	GAD1- or GABA-B-targeted mouse models	Tumor-derived GABA signals beyond classical neurotransmission can be pharmacologically targeted to reverse immunosuppression

Table 1 (continued)

Ref. no	Neurotransmitters studied	Results obtained	Model used	Key findings
48	γ-Aminobutyric acid (GABA)	B cell-derived GABA promoted monocyte differentiation into anti-inflammatory macrophages secreting IL- 10 and suppressing CD8 + T cell cytotoxicity	Activated B cells and plasma cells	GABA-A receptor blockade enhances CD8 + T cell infiltration and synergizes with anti-PD1 therapy
49	γ-Aminobutyric acid (GABA)	Tumor incidence was comparable between metaphane and nembutal groups in HT29-injected mice, but combined tumor weight (primary + metastasis) was significantly higher in metaphane group (1.61 ± 0.45 g vs. 0.07 ± 0.05 g; $P = 0.008$)	KM12SM, HT29, RKO colon cancer cell lines	GABA receptor agonists inhibit primary and metastatic colon cancer
51	Adrenaline/noradrenaline	Adrenaline increased HT29 cell proliferation and reduced cisplatin-induced apoptosis	HT29 cells	The adrenaline-NFκB-miR- 155 pathway partially mediates stress-induced HT29 proliferation and chemoresistance
52	Adrenaline/noradrenaline	β2-Adrenergic receptors significantly correlated with tumor grade, size, invasion, and lymph node metastasis ($P < 0.05$), but not with gender, CRC location, or gross appearance ($P > 0.05$)	Human tissue samples	β2-Adrenergic receptors influence CRC cell proliferation, migration, and invasion
53	Adrenaline/noradrenaline	NE-induced phosphorylation of CREB1 promoted proliferation, migration, and invasion in human colon cancer cells	Colon cancer cells	NE drives CRC metastasis via CREB1-miR-373 axis activation
54	Adrenaline/noradrenaline	COX- 2 expression was elevated in mammary tumors of chronically stressed mice	Adrenaline- and TNFα-exposed human macrophages	Adrenergic signaling promotes CRC immune evasion by increasing macrophage COX- 2/IL- 10 expression, suppressing CD8 + T cell proliferation and IFN-γ production
56	Adrenaline/noradrenaline	Adrenaline stimulated HT- 29 cell proliferation	HT- 29 human colon adenocarcinoma cells	Adrenaline stimulates HT- 29 proliferation via COX- 2-dependent pathways through β1- and β2-adrenergic receptors
57	5-Hydroxytryptamine (5-HT)	Enteric neurons are required for CSC self-renewal and colorectal tumorigenesis	Colorectal cancer stem cells (CSCs)	Crosstalk between enteric neurons and tumor cells drives CRC development
58	5-Hydroxytryptamine (5-HT)	5-HT levels and TPH1 expression were significantly upregulated in CRC tissues	CRC patients and mouse models	Targeting the 5-HT/NLRP3 positive feedback loop may provide therapeutic opportunities
59	5-Hydroxytryptamine (5-HT)	5-HT(1D)R antagonist GR127935 effectively inhibited metastasis via Axin1 targeting	Orthotopic CRC mouse models	A 5-HT/NLRP3 positive feedback loop in the CRC microenvironment promotes tumor progression
61	5-Hydroxytryptamine (5-HT)	SERT expression correlated with YAP in CRC tissues, and serum 5-HT levels were significantly elevated in CRC patients	Human colon cancer cells	Serotonin activates RhoA/ROCK/YAP signaling via SERT to promote CRC oncogenesis
62	5-Hydroxytryptamine (5-HT)	Significant inverse correlation between SSRI use and CRC risk	Cohort studies	SSRI use is associated with reduced CRC risk in individuals with family history

Table 1 (continued)

Ref. no	Neurotransmitters studied	Results obtained	Model used	Key findings
64	5-Hydroxytryptamine (5-HT)	TIAM2S altered immunity via T lymphocyte amplification, particularly marked in CD8 + T cells combined with CXCL13/BCA- 1 chemokines in TIAM2S-TG mice	TIAM2S-overexpressing mouse models	TIAM2S induces a pro-inflammatory immune microenvironment via serotonin-driven immunomodulation, facilitating colorectal tumorigenesis

This table synthesizes evidence from 27 studies on the role of neurotransmitters in colorectal cancer (CRC), emphasizing their dual impact on tumor-intrinsic pathways (e.g., proliferation, metastasis) and immune microenvironment reprogramming (e.g., immunosuppression, immune evasion). It serves as a concise overview of key mechanisms and potential therapeutic targets to guide research and clinical strategies in CRC treatment

Immune cells can activate toll-like receptors (TLRs) through pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) released by host-damaged cells, triggering a cascade of signaling events that ultimately lead to the synthesis and release of pro-inflammatory cytokines [72]. Toll-like receptors, including TLR3, TLR4, TLR7, and TLR9, have been found to be expressed in sensory neurons, allowing them to sense danger signals and pathogens and to function in the control of pain and itch [73].

Furthermore, cytokines can be detected by afferent fibers of the autonomic nervous system and relayed to the brain, forming a communication "neural" pathway [74]. Peripheral immune signals can also be transmitted through a "humoral" pathway, where cytokines directly reach the brain parenchyma and modulate central brain function. This communication mechanism is more likely to occur under inflammatory conditions where the blood–brain barrier becomes highly permeable, as cytokines can be more readily transported to the brain [75] (Fig. 2).

Undoubtedly, the neuroimmune crosstalk plays a role in various parts of the body, so it is unsurprising that it is increasingly recognized as an important regulatory factor for digestive function and gastrointestinal homeostasis. However, there is limited understanding of the mechanisms of neuroimmune interaction in the context of gastrointestinal cancers, necessitating further research.

Current status of targeted neurotherapy in colorectal cancer

In recent years, research on therapeutic strategies has focused on metastatic colorectal cancer (CRC). For decades, systemic chemotherapy, including drugs such as 5-fluorouracil and oxaliplatin, has been the primary intervention to prolong patient survival, yet the 5-year survival rate remains low. Targeted therapies are designed to specifically act on proteins involved in the proliferation, growth, and metastasis of cancer cells. Their efficacy, however, is predicated on the presence of relevant protein or gene mutations. The Wnt signaling pathway is involved in the regulation of the central nervous system and is widely believed to be associated with the pathogenesis of CRC primarily due to the aberrant activation of Wnt/β-catenin signaling [76]. Studies have shown that knocking down RHBDD1 can attenuate the activity of the Wnt signaling pathway and the protein levels of β-catenin, thereby inhibiting CRC metastasis. Although the upstream regulatory mechanisms of RHBDD1 in the Wnt pathway remain incompletely elucidated, its role as a transmembrane protein warrants attention as a therapeutic target, potentially serving as a novel strategy to suppress CRC metastasis [77]. In the EGFR pathway, cetuximab

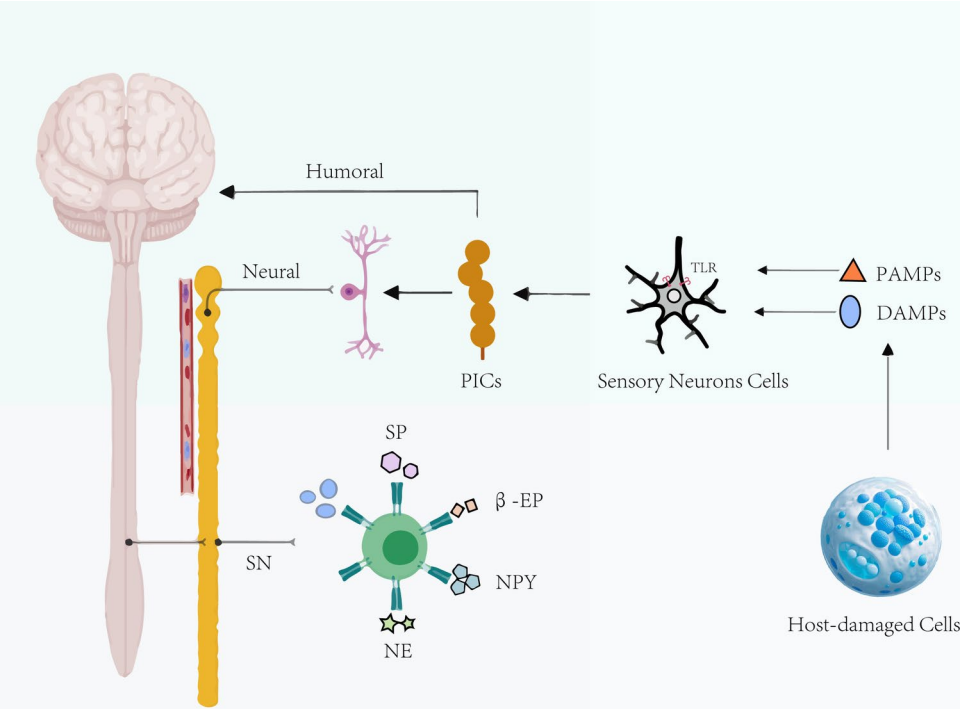

Fig. 2 The interaction between the nervous system and the immune system. Immune cells are activated via toll-like receptors (TLRs) localized on sensory neurons cells that recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) released from host-damaged cells, thereby triggering a signaling cascade that culminates in the release of pro-inflammatory cytokines (PICs). These cytokines subsequently exert influence on the central nervous system (CNS) through both humoral circulation and neural circuitry. Simultaneously, neurotransmitters including substance P (SP), β-endorphin (β-EP), norepinephrine (NE), and neuropeptide Y (NPY) may participate in signal transduction processes and demonstrate modulatory roles in inflammatory responses

combined with chemotherapy has been targeted for treating patients with metastatic CRC [78]. However, studies indicate that RAS mutations may lead to the erroneous activation of RAS/RAF/MAPK signaling, affecting the efficacy of EGFR inhibitors [79]. Concurrently, different targeted therapies should be devised for various molecular subtypes and primary tumor laterality, such as anti-EGFR therapy combined with doublet chemotherapy as a first-line treatment for untreated RAS wild-type mCRC [80]. Therefore, molecular analysis of tumors is essential in treating metastatic CRC to improve overall survival rates. Given that systemic chemotherapy has been the conventional first-line treatment for CRC for decades—bearing systemic toxicity and low specificity for individual patient selection—and due to intrinsic changes in tumors, including induced genetic mutations in target pathways and aberrant activation of compensatory signaling pathways, resistance to targeted therapies has emerged. Patients with metastatic CRC often receive cetuximab treatment; research has found that TrkB blockade can enhance the inhibitory effect of cetuximab on CRC cell proliferation and survival [80], indicating that the TrkB/BDNF pathway could serve as a potential therapeutic target. At the same time, preliminary progress has been made in strategies to reverse anti-EGFR therapy resistance, including the development of new EGFR-targeted inhibitors, combination multi-target inhibitors, and metabolic modulators [81]. Currently, for targeted treatment of CRC, we still require more molecular biomarkers and therapeutic targets to combat various mutations and drug resistance in CRC cells. Furthermore, targeted drug combinations based on molecular analysis are needed to improve patient outcomes in CRC.

Conclusions and future perspectives

This comprehensive review elucidates the intricate neuro-oncological pathways driving colorectal cancer progression. It delineates how neural components—including neurotransmitters, neurotrophic factors, and intracellular signaling cascades—modulate cancer hallmarks including sustained proliferation, invasion, stemness, and treatment resistance. For instance, the neurotransmitter serotonin promotes tumor growth and metastasis via paracrine and autocrine stimulation, while neurotrophic mediators like NGF and BDNF activate oncogenic signaling via tropomyosin receptor kinase receptors. Downstream pathways, like Wnt/β-catenin signaling, further link neural activity with cancer aggression. These mechanistic insights illuminate promising therapeutic

directions; strategies targeting rate-limiting serotonin synthesis, key serotonin receptors, neurotrophic cascades, and neural-cancer signaling may suppress tumorigenesis. As research continues unraveling this intricate signaling network, opportunities will emerge to develop specialized therapies selectively targeting the neural underpinnings of cancer.

Future efforts should concentrate on translating these biological insights into novel clinical interventions that improve patient outcomes. By comprehensively mapping—and ultimately therapeutically leveraging—neural mechanisms governing treatment response, more precise and less toxic therapeutic regimens may be attainable. Elucidating the neuro-oncological interface in colorectal cancer thus holds tremendous potential for catalyzing breakthrough precision oncology and meaningfully improving patient survival. Further exploration of this intricate signaling nexus between neural mediators and cancer pathogenesis promises to inform pioneering therapeutic modalities that selectively disrupt non-malignant support mechanisms upon which tumors rely. This continued elucidation of neuro-colorectal cancer crosstalk is imperative for developing specialized therapies that selectively target the neural underpinnings of cancer aggression.

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